Purinergic Signalling (2023) 19:229–243
https://doi.org/10.1007/s11302-022-09856-4

REVIEW ARTICLE

Purinergic signaling in myocardial ischemia–reperfusion injury

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Received: 2 November 2021 / Accepted: 18 February 2022 / Published online: 7 March 2022

Abstract
Purines and their derivatives, extensively distributed in the body, act as a class of extracellular signaling molecules via a rich array of receptors, also known as purinoceptors (P1, P2X, and P2Y). They mediate multiple intracellular signal transduction pathways and participate in various physiological and pathological cell behaviors. Since the function in myocardial ischemia–reperfusion injury (MIRI), this review summarized the involvement of purinergic signal transduction in diversified pathological processes, including energy metabolism disorder, oxidative stress injury, calcium overload, inflammatory immune response, platelet aggregation, coronary vascular dysfunction, and cell necrosis and apoptosis. Moreover, increasing evidence suggests that purinergic signaling also mediates the prevention and treatment of MIRI, such as ischemic conditioning, pharmacological intervention, and some other therapies. In conclusion, this review exhibited that purinergic signaling mediates the complex processes of MIRI which shows its promising application and prospecting in the future.

Keywords Myocardial ischemia–reperfusion injury · Purinergic signaling · Pathological processes · Cardioprotective interventions

Introduction

As the most frequently occurring cardiovascular disease, myocardial ischemia poses a serious threat to human health owing to its high morbidity and mortality [1]. Therefore, it has been a pressing issue to the prevention and treatment of myocardial ischemia effectively. Currently, the main treatment for acute myocardial infarction (AMI) includes drug therapy, surgical coronary artery bypass grafting, and percutaneous coronary intervention (PCI). Bypass surgery and PCI are used to eliminate vascular blockage and restore normal vascular perfusion, which can greatly reduce the mortality of AMI. However, cardiac tissue damage is aggravated after reperfusion, which is called myocardial ischemia–reperfusion injury (MIRI) [2, 3]. This phenomenon also can be observed in other cardiac surgeries, such as valve replacement, heart transplantation, and surgery for congenital heart disease. Undoubtedly, further cardiac dysfunctions will be induced by this type of injury, such as myocardial stunning, reperfusion arrhythmia, myocyte death, and endothelial and microvascular dysfunction, including the no-reflow phenomenon and inflammatory response [4]. Moreover, it was reported that lethal reperfusion injury accounts for up to 50% of the final myocardial infarct size [5]. Consequently, MIRI is a grave, unsolved problem that hinders AMI patients from obtaining the best curative treatment.

Accumulating evidence indicates that purinergic signaling has great therapeutic potential against MIRI. Purinergic signaling involves purines and their derivatives, most notably adenosine and ATP, which were first considered as a class of extracellular signaling molecules by Geoffrey Burnstock in 1972 [6]. They are quite different from classic adrenergic and cholinergic neurotransmitters. By 1978, Burnstock proposed two separate families of receptors for purines, named P1 and P2 receptors [7]. P1 receptors are mainly activated by adenosine (ADO), while P2 receptors

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are activated by adenosine 5'-triphosphate (ATP) and adenosine 5'-diphosphate (ADP), uridine triphosphate (UTP), and uridine diphosphate (UDP). This theory has not been widely accepted until most purinergic receptors were cloned and characterized in the early 1990s [8]. To date, there have been four G protein-coupled subtypes of P1 receptors (A1, A2A, A2B, and A3), which are related to intracellular levels of cyclic adenosine monophosphate (cAMP). The four receptors are different from each other. The A1 and A3 signaling pathways are linked to inhibitory G proteins to downregulate cAMP, while the A2A and A2B signaling pathways are linked to stimulatory G proteins to upregulate cAMP. A1 and A2A have the highest affinity to ADO, and A3 and A2B have the lowest affinity to ADO [9]. Their activation depends on ADO concentration. The P2 receptors are a little more complicated and contain seven ion channel subtypes of P2X receptors (P2X1-7) and eight G protein-coupled subtypes of P2Y receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y). They are diffusely expressed in almost every system in the human body, which mediates multiple intracellular signal transduction pathways and triggers various cell behaviors since the abnormal purinergic signaling will result in a wide range of diseases, like neurological, rheumatic, cardiovascular, and cancer diseases [10]. In MIRI, as soon as the cardiac tissue is subjected to ischemic injury, intracellular ATP is released from the affected cells and gradually breaks down to ADP, adenosine 5'-monophosphate (AMP), and ADO. These endogenous ligands bind to and act on purinergic receptors in the cardiovascular system and associated circulating cells, thereby participating in the complicated pathological processes of MIRI. In this review, we will examine the role of purinergic signaling in MIRI and its application in clinical.

Expression of purinergic receptors in the cardiovascular system and associated immune cells

Since the first report on the effects of adenine compounds on disturbed cardiac rhythm was published in 1929 [11], thousands of articles on purinergic signaling in the cardiovascular system have emerged. Scientists have found that numerous cells in the heart and blood vessels can express one or more subtypes of purine receptors that affect heart function modulation, vascular tone, angiogenesis, and inflammation. Existing evidence has shown that the four P1 subtypes are differentially expressed in cardiomyocytes, cardiac fibroblasts, coronary vascular, and inflammatory cells, which mediate a range of generally beneficial actions [12]. Specifically, cardiomyocytes, endothelial cells, and vascular smooth muscle cells express all four P1 subtypes. Cardiac fibroblasts express the A2A and A2B subtypes; however, pericytes express the A1 and A2A subtypes. As for inflammatory cells, polymorphonuclear leukocytes express all four P1 subtypes, but mast cells and macrophages only express the A2A and A3 subtypes. They usually play a vasodilatory and cardioprotective role inside the body. Some studies suggest that almost all subtypes of P2X receptors are expressed in cardiomyocytes [13]. Furthermore, P2X1, P2X2, and P2X4 are expressed in vascular smooth muscle cells and endothelial cells, which contribute significantly to vascular contraction and relaxation responses, respectively [14]. The distribution of P2Y receptors is similar to that of P2X receptors. Some reviews reveal that many P2Y subtypes are also expressed in cardiomyocytes, including P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11 [13, 15]. It is interesting to note that P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11 are expressed in the vascular endothelium [14, 16], while P2Y2, P2Y4, P2Y6, and P2Y14 are expressed in the vascular smooth muscle [13, 17, 18]. All of the aforementioned P2Y subtypes participate in vascular contraction and relaxation. Furthermore, P2 receptors are expressed in erythrocytes, platelets, and immune cells, which play a major role in multiple physiological and pathological changes associated with cardiovascular diseases [13, 19]. The expression of purinergic receptors in the cardiovascular system cells and associated immune cells is summarized in Fig. 1.

Purinergic signaling in pathological processes of MIRI

The microcirculation disturbance and surrounding tissue injury caused by myocardial ischemia–reperfusion cover the ischemic period, acute and subacute periods during reperfusion, and the chronic injury period after reperfusion. The disorder of energy metabolism initiates the pathological process of MIRI and results in the reduction of ATP synthesis furtherly in the ischemic period. In addition, the accelerating ATP deficiency in the intravascular and perivascular tissues, which, due to the continuous consumption of ATP by blood vessels and surrounding tissues, induces serious cytoskeleton depolymerization and cell necrosis. After the blocked blood vessels are recanalized, the injury enters the early stage of reperfusion. During this period, the supply of oxygen and nutrients is restored, and peroxide is produced in excess which acts in two aspects. On one side, the DNA and membrane structure of cardiac cells suffer great damage owing to lipid peroxidation. On the other side, peroxide triggers the release of inflammatory factors and increases the expression of adhesion molecules, which induce acute pathological changes, such as exudation, bleeding, thrombosis, and cell apoptosis. Within 24 h to 7 days after reperfusion, the damaged vascular endothelial cells and perivascular tissues release

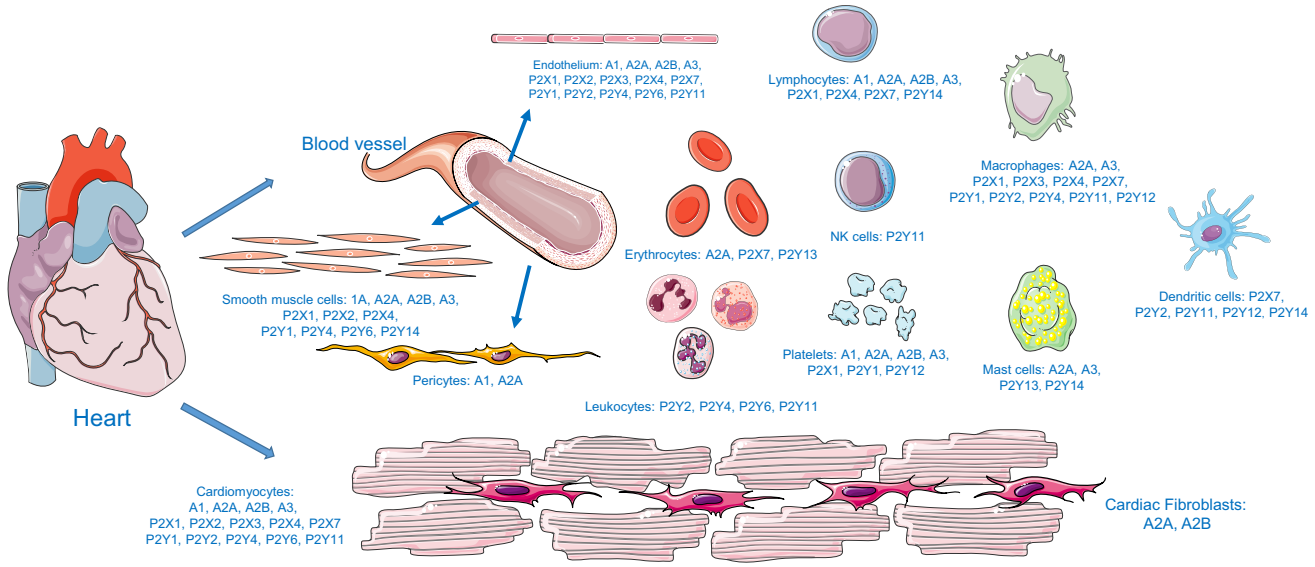

Fig. 1 Expression of purinergic receptors in the cardiovascular system and associated immune cells

multiple chemokines and transforming growth factors. These substances induce collagen deposition by acting on fibroblasts and trigger the remodeling of perivascular tissue, which leads to the induction of a subacute pathological process dominated by organ fibrosis. After 7 days of reperfusion, some lymphocytes swim out of the blood vessels and contribute to the perivascular chronic inflammatory process. Based on the aforementioned results, it can be suggested that the complex pathological processes of MIRI can be roughly divided into the following categories: energy metabolism disorder, oxidative stress injury, calcium overload, inflammatory immune response, platelet aggregation, coronary vascular dysfunction, and cell necrosis and apoptosis. In this review, we will focus on the role of purinergic signaling in the aforementioned MIRI pathological processes, as it may reveal great therapeutic

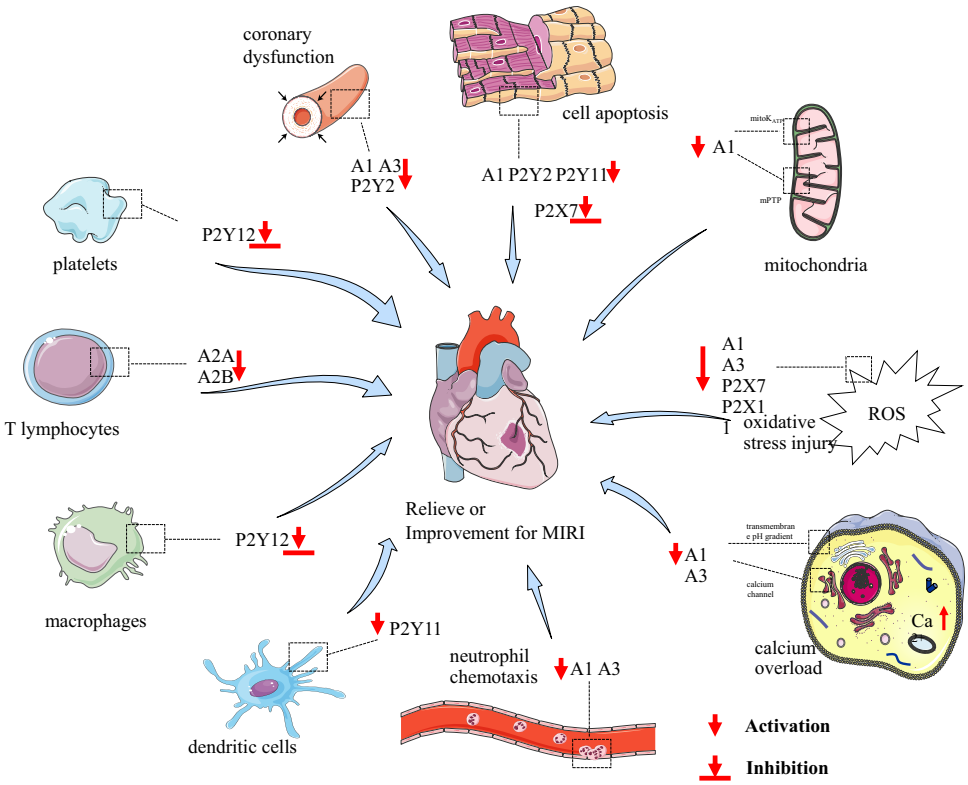

Fig. 2 Purinergic signaling in pathological processes of MIRI

potential and help develop new therapeutic agents for MIRI (Fig. 2).

Energy metabolism disorder

As previously described, the energy metabolism disorder is the initial contributing factor to MIRI [20]. The normal function of cardiomyocytes is inextricably linked to the energy provided by ATP. During the ischemic period, the energy metabolism of the ischemic myocardium will change from aerobic oxidation to anaerobic glycolysis when the coronary blood flow decreases to a certain extent, which reduces ATP production and energy supply. In this situation, the cardiomyocytes are in a state of energy starvation, thus inducing serious cardiac dysfunction. Simultaneously, anaerobic glycolysis results in a great increase in intracellular lactic acid levels, which leads to a decrease in pH and accelerates the acidosis of cardiomyocytes. No doubt, those trigger a series of pathological changes. It is worth noting that the energy metabolism disorder also occurs throughout the reperfusion period owing to the mitochondrial damage caused by ischemia. Therefore, the timely treatment of the myocardial energy metabolism disorder is an important method to alleviate MIRI. As early as the 1980s, scientists found that the administration of exogenous ADO could increase ATP levels in the post-ischemic myocardium [21], a phenomenon that could not be replicated in in vivo models [22]. Moreover, ADO could also stimulate myocardial glycolysis, which maintains cell viability by increasing the cellular uptake of glucose [23, 24]. This protective effect may be mediated by the P1 receptor. For example, some studies have found that the overexpression of the A1 receptor can reduce ATP loss and improve the bioenergetic state during severe ischemic insult and reperfusion, which may contribute to improved functional tolerance [25]. This protective effect of the A1 receptor may be mediated by the activation of the intrinsic mitochondrial K_{ATP} channel, which is a core link of energy metabolism in cardiomyocytes [26–28]. A recent study suggested that the remote cardioprotective effect of the transfer of coronary effluent from an ischemic preconditioned heart is mediated by P1 receptor activation, which preserves mitochondrial integrity and function in cardiomyocytes [29]. Therefore, purinergic signaling may be a potential target for alleviating energy metabolism disorders in MIRI.

Oxidative stress injury

Reactive oxygen species (ROS) incur important pathological changes in two aspects in MIRI. On the one hand, ROS can reduce the activities of Na/K ATPase and Ca^{2+} ATPase and cause lipid peroxidation, which damages the cell membrane directly and destroys the integrity of the cardiomyocytes causing myocardial necrosis and apoptosis. On the other hand, ROS initiate the expression of inflammatory mediators, resulting in neutrophil infiltration and capillary injury. This excessive inflammatory reaction is another significant pathological change that aggravates the myocardial injury. Furthermore, ROS can create a dissipation of the mitochondrial membrane potential and induce long-term opening of the mitochondrial permeability transition pore (mPTP), which inevitably leads to cell energy metabolism disorder. Thus, based on this point, it is believed that the inhibition of excessive oxidative stress is a vital strategy for MIRI prevention and treatment. A large amount of studies show that overexpressing the A1 receptor can preserve mitochondrial function and salvage cardiomyocytes from cell death by inhibiting the opening of mPTP and modulating K_{ATP} channels in MIRI [30, 31]. Similarly, the activation of A3 receptor activation can regulate K_{ATP} channels to attenuate post-ischemic dysfunction and provide cardioprotection [32, 33], which may involve the activation of the NF-κB, transcription of iNOS, and synthesis of NO in the heart [34, 35]. In addition to the P1 receptor, P2 subtypes also contribute to oxidative stress injury in MIRI. For example, one study showed that extracellular ATP addition at the reoxygenation stage confers a cardioprotective effect against hypoxia/reoxygenation injury, which is mediated by the P2Y11 receptor in human cardiomyocytes via reducing mitochondrial ROS production and activating the PKCε signaling pathway [36]. In addition, the pannexin-1/P2X7 compound can be activated in MIRI, which promotes the release of endogenous cardioprotectants, such as adenosine and sphingosine 1-phosphate. These substances can trigger a protective effect through the PI3k/Akt survival pathway to delay mPTP opening and reduce myocardial apoptosis [37]. Thus, purinergic signaling plays a major role in oxidative stress injury in MIRI.

Calcium overload

Changes in intracellular calcium homeostasis play an important role in MIRI. Under physiological conditions, the concentrations of intracellular and extracellular calcium ions are relatively stable. Once myocardial cells are ischemic and hypoxic, metabolism shifts from cellular respiration to anaerobic glycolysis, causing a transmembrane pH gradient change. Abundant sodium ions flow into the cells. When the reperfusion stage occurs, the energy supply is restored, and the pH gradient returns to normal. This recovery promotes the transmembrane exchange of sodium and calcium ions. Finally, the influx of extracellular calcium into cells results in calcium overload This is a potential mechanism for oxygen-free radical and neutrophil infiltration, which is also closely related to cardiac purinergic signaling. Some studies have revealed that cardiac A1 receptor overexpression is associated with a decreased rate of active calcium

transport into the sarcoplasmic reticulum [38]. This reduction in active calcium uptake can contribute to increased myocardial resistance to ischemia. Interestingly, the A3 receptor has a similar modulation effect on calcium channels in the sarcoplasmic reticulum, thereby exerting a myocardial protection effect against MIRI [39]. Purinergic signaling is a conventional therapeutic target for intracellular calcium homeostasis in MIRI.

Inflammatory immune response

The activation of inflammatory immune response is another crucial pathological change during MIRI; in the early stage of reperfusion, injured cardiomyocytes activate the innate immune response, which induces various inflammatory factors and chemokines releasing, and creating a pro-inflammatory environment finally. Some circulating inflammatory cells, such as neutrophils, macrophages, and lymphocytes, are recruited at the site of the injured myocardium both directly and indirectly. This infiltration aggravates and spreads the inflammatory response. Approximately 4 days later, the injured cardiomyocytes exhibit anti-inflammatory and restorative properties. During this pathological change, multiple anti-inflammatory and immunosuppressive factors are released which promote vascular regeneration and myocardial tissue repair. In this long and complicated period, purinergic signaling plays both a positive and negative regulatory role via selective receptor activation. However, there are controversies among studies about the role of purinergic signaling. For example, some studies have suggested that the activation of the A_1 receptor can stimulate neutrophil chemotaxis [40], which promotes a pro-inflammatory immune response in MIRI. However, other studies have shown that the overexpression of the A1 receptor can lower the levels of tissue myeloperoxidase activity, an index of neutrophil accumulation, thus resulting in smaller infarct size in MIRI [41]. Moreover, the result of one study has verified that A_3 receptor activation can attenuate MIRI by decreasing neutrophil-endothelial cell interactions [42]; however, the results of other studies suggest that the activation of the A3 receptor leads to pro-inflammatory activity and contributes to MIRI [43, 44]. A2 receptor subtypes are considered more involved in inflammatory immune responses in ischemia–reperfusion injury. CD73 on T cell-derived adenosine acts on A2A and A2B receptors in an autocrine and paracrine manner [45]. The activation of A2A and A2B receptors can inhibit the release of pro-inflammatory cytokines, including TNF-α, INF-γ, IL-1α, IL-1β, IL-2, and IL-6. In contrast, some anti-inflammatory cytokines, such as IL-10, are secreted via the stimulation of the A2A receptor [46, 47]. Furthermore, P2 receptors are also important players in this pathological change. For instance, some studies have reported that pro-inflammatory factors, such as IL-1β, IL-18, and ROS, can be secreted excessively via the P2X7 receptor [48–50]. The potential mechanism may be the K^+ efflux and Ca^{2+} influx induced by the openness of the P2X7 receptor, which triggers NLRP3 inflammasome assembly and then converts pro-caspase-1 into active caspase-1. This inflammatory response of the P2X7 receptor contributes to myocardial injury and myocardial fibrosis, which results in decreased cardiac function [51]. Paradoxically, some other studies revealed that P2X7/pannexin-1 pore mediated the cardiac protective effect of conditioning intervention; thus, the inhibition of pannexin-1 or P2X7 could abrogate the protective effect of ischemia–reperfusion conditioning and result in increased infarct sizes [52–54]. Furthermore, the P2Y11 receptor in human dendritic cells also plays a pivotal role in mediating the inflammatory response following ischemia–reperfusion injury, which could be beneficial in AMI [55]. The stimulation of this subtype could also modulate the secretome of cardiac fibroblasts, regulate inflammatory immune reactions, and reduce hypoxia/reoxygenation injury [56]. Another important purinergic receptor is P2Y12. One study verified that P2Y12 inhibition in macrophages can attenuate inflammation and cardiac remodeling induced by MIRI [57]. Based on the aforementioned, the knowledge between purinergic signaling and multiple inflammatory immune cells needs to be furtherly explored to understand their roles and mechanisms.

Platelet aggregation

Platelet aggregation has recently emerged as a popular pathological symptom of MIRI. Activated platelets may aggregate and form microthrombi in small cardiac vessels and capillaries, leading to cardiac tissue damage. Activated platelets also contribute to reperfusion injury by enhancing platelet-leucocyte aggregation, the release of potent vasoconstrictors, and the secretion of pro-inflammatory molecules [58]. So far, three subtypes of P2 receptors in platelets have been recognized, including two receptors of ADP (P2Y1 and P2Y12) and one of ATP (P2X1), which are all involved in platelet aggregation. Therefore, the pharmacological inhibition of platelets is considered a standard treatment for AMI patients, especially by P2Y12 receptor inhibitors. Among these inhibitors, clopidogrel is the most commonly used drug in clinics, which effectively reduces coronary occlusion without thrombus formation and is recommended by many clinical guidelines [59]. Scientists have found that a few newly discovered P2Y12 inhibitors, such as prasugrel [60], cangrelor [61, 62], and ticagrelor [63], exhibit great ability to ameliorate myocardial damage beyond their well-studied anti-thrombotic effects. However, it does not mean that clopidogrel can be replaced completely. Recent trials have shown that in patients aged 70 years or older who suffered

high bleeding risk, clopidogrel is a favorable alternative to ticagrelor and prasugrel as it leads to fewer bleeding events without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke, and bleeding [64–66]. However, the potential mechanism of action of clopidogrel, which seems to extend beyond platelet inhibition, has not yet been fully explored. Some studies have reported that the cardioprotective effect of cangrelor is dependent on platelets, sphingosine phosphorylation, and certain other blood components [67, 68]. Prasugrel can reduce ischemia-induced ventricular arrhythmias via PI3k/Akt signaling pathways [69]. Ticagrelor can block the adenosine re-uptake transporter ENT1, thereby raising tissue adenosine levels to reduce cardiac injury [70, 71]. Therefore, it is worthwhile to pay more attention to purinergic signaling in platelet function during MIRI.

Coronary vascular dysfunction

Previous studies have verified that ischemia–reperfusion can generate substantial coronary vascular events, such as vasospasm, thrombosis or re-stenosis, and endothelial injury. These dysfunctions contribute significantly to myocardial depression and impaired cardiac reflow, which are the key determinants of infarct size in MIRI. Given the specific vascular protective effect of ADO, scientists have attempted to explore the relevance of purinergic signaling in coronary vascular dysfunction. In the case of the P1 receptor, some studies have shown that vascular injury is intrinsically limited by the endogenous activation of the A1 receptor, while the exogenous A3 receptor activation further limits post-ischemic dysfunction [72]. Thus, the pretreatment with an agonist of the A1 receptor can alter the spatial distribution of myocardial blood flow, which might reflect a downregulation of metabolic state, thereby contributing to cardioprotective effects [73]. Even more, the coronary microvascular tone can also be activated by receptors of A2A and A2B. Adenosine-mediated. Previous research revealed that ischemia–reperfusion can attenuate coronary vasodilatation induced by the A2A agonist in the dog [74]. What is more, A2B-mediated relaxation in isolated coronary small arteries can also be blunted in swine with myocardial infarction [75]. The downstream targets of P1 receptors are H_2O_2, K_{ATP}, K_V, and K_{Ca2+} channels [76]. Besides, the increased extracellular ATP level after the ischemic injury can also protect heart endothelial cells against acute reperfusion injury [77]. Another study has suggested that the coronary endothelium-dependent relaxation may be partly mediated by P2 receptors after ischemia–reperfusion [78]. For example, the P2Y2 receptor on the coronary artery can be reduced to minimize coronary contraction following ischemia–reperfusion injury [79]. Therefore, purinergic receptors may represent new avenues for the treatment of MIRI resulting from coronary vascular dysfunction.

Cell necrosis and apoptosis

Cell necrosis and apoptosis are the most direct pathological manifestations of MIRI. Both terms describe different types of cardiac cell death. Cell necrosis refers to passive death caused by physical or chemical damage injuries, such as hypoxia and malnutrition. Cell apoptosis is also known as programmed cell death, refers to cell death controlled by apoptosis genes activated by certain conditions, and is a useful strategy for better adaptation to the living environment. These pathological processes can be modulated by purinergic signaling. Numerous clinical trials have verified that ADO infusion can result in a significant reduction in infarct size [80, 81]. This cardioprotective effect is mainly mediated by P1 receptors. For example, some studies have reported that the stimulation of the A1 receptor can reduce necrosis and infarct size in MIRI [41, 82] and inhibit cardiac cell apoptosis by regulating the expression of Bcl-2/Bax and caspase 3 and their activity [83–85]. In addition, P2 receptors are also involved in cell death in MIRI. For example, P2X7 plays a role in myocardial impairment by increasing apoptosis, while the administration of a specific P2X7 receptor antagonist can reduce the HSP70 protein levels in cardiac cells [86]. In contrast, the P2Y2 receptor may exert a protective effect against MIRI. A treatment with a specific P2Y2 receptor agonist reduces cell death and increases the expression of the anti-apoptotic protein Bcl-2 [86]. These two regulatory agents can decrease the pro-apoptotic protein caspase-8 levels [86]. A recent study revealed that the stimulation of the P2Y11 receptor can also reduce the apoptotic markers after cardiac transplantation, such as the Bax/Bcl-2 ratio, which results in significantly prolonged cardiac allograft survival [87]. All these results suggest that purinergic signaling is closely related to cell necrosis and apoptosis, which are the last, but not least, pathological links to MIRI.

Purinergic signaling in cardioprotective interventions for MIRI

Purine signaling has become a potential target for the prevention and treatment of MIRI, owing to its involvement in the multiple pathological manifestations of MIRI. Thus far, we reviewed the various interventions reported and found that many of them employ purinergic signaling as action mechanisms (Table 1).

Table 1 Purinergic signaling in cardioprotective interventions in MIRI

	Ischemic conditioning	Pharmacological interventions								Other therapies				
		Clopidogrel, prasugrel, cangrelor, ticagrelor	Neutrophil-derived netrin-1	Alogliptin	Vitamin B6 pyridoxal 5-phosphate	miR-150	Metformin	Dipyridamole	Intrathecal morphine preconditioning	Mycelia of *Cordyceps sinensis*	Resveratrol	Alcohol	Aerobic exercise	Electro-acupuncture
A1	√			√			√	√	√	√	√	√		
A2A	√													√
A2B	√		√											√
A3	?													
P2X7	√					√					√		√	
P2Y6					√									
P2Y11					√									
P2Y12		√												

Ischemic conditioning

Ischemic conditioning is a crucial intervention in MIRI, including ischemic preconditioning, ischemic postconditioning, and remote ischemic conditioning (pre and post). Each preconditioning has its own merits. Ischemic preconditioning was first discovered in 1986 [88, 89]. Some physicians have discovered that preconditioning the myocardium using short episodes of sublethal ischemia could delay the onset of necrosis during a subsequent lethal ischemic insult. Since then, scientists have been trying hard to explore the underlying mechanism of this endogenous myocardial protection effect. To date, they have reached the following consensus: the protective effect produced by ischemic preconditioning includes early preconditioning and the second window of protection. Early preconditioning refers to infarction delayed by 1–2 h after the first ischemic stimulation, while the second window of protection refers to a protective effect that lasts 12–72 h [90]. ADO is considered a classic trigger and mediator [91] that is involved in the preconditioning of rabbit [92], dog [93], pig [94], and human myocardia [95]. This cardioprotective effect of ADO in preconditioning is related to all P1 receptor subtypes. Among them, A1 and A3 receptors can not only modulate the activation of the mitochondrial K_{ATP} channel and the opening of mPTP in cardiomyocytes [96, 97], but also activate phospholipase C or protein kinase C (PKC) directly [98–100]. However, some researchers still claim that the A_3 receptor is not necessary for ischemic preconditioning, as it may incur injury in MIRI; thus this requires more in-depth research in the future [101]. The myocardial protective mechanisms of A2A and A2B receptors are completely different. Some researchers have suggested that A2A may inhibit endothelial-neutrophil interactions in MIRI [102], while A2B activation reduces MIRI by promoting anti-inflammatory macrophage differentiation via the PI3K/Akt pathway [103, 104]. Subcellular ERK isoform signaling is also involved in P1 receptor preconditioning to reduce myocardial infarct size, especially via the A1 and A2A receptors [105]. In 1993, researchers confirmed that ischemic preconditioning and its protective effect can occur between different parts of the same organ or between different organs, which was proposed as remote ischemic conditioning [106]. In 2003, it was shown that brief cycles of coronary occlusion during the early minutes of reperfusion can reduce the infarct size, which becomes equivalent to that seen after ischemic preconditioning [107]. These two interventions have emerged as novel therapeutic strategies for MIRI, but the underlying mechanisms remain unclear. Some studies have shown that this cardioprotective effect is associated with the activation of the PI3K/Akt pathway and the prevention of mPTP formation via the

A2B receptor during reperfusion [108, 109]. Furthermore, the pre- and postconditioning of P2X7 receptor agonists can protect the heart against ischemia–reperfusion injury by opening pannexin-1/P2X7 channels [53].

Pharmacological intervention

The development of pharmacology has enhanced the exploitation of many adjuvant drugs for purinergic receptors. The emergence of these drugs is not only convenient for laboratory research, but also is the potential to play a role in clinical application against MIRI, especially in terms of selective agonists and antagonists acting on various receptor subtypes. The most well known are P2Y12 inhibitors, such as clopidogrel [110], prasugrel [69], cangrelor [68], and ticagrelor [63], which have been discussed in detail in a previous section of this review. It is worth noting that purines coexist with other classical transmitters, thereby purinergic receptors have multiple cross-talk with other signaling pathways. In other words, some non-purinergic molecules can also activate purinergic receptors and exert the same cardioprotective effect against MIRI. For instance, neutrophil-derived netrin-1 attenuates MIRI through myeloid adenosine A2B signaling [111]. The same cardioprotective effect has been observed in the dipeptidyl peptidase 4 inhibitor, alogliptin, which suppresses MIRI via the A1-PKC-CREB signaling pathways [112]. P2Y11 and P2Y6 receptors are candidate receptors of cardiac pharmacological preconditioning induced by vitamin B6 and its metabolite, pyridoxal 5-phosphate [113], which may be associated with the reduction of sarcoplasmic reticulum Ca^{2+} transport activities [114].

Additionally, one recent study affirmed that some circulating micro-RNAs, such as miR-150, protect the heart from ischemic injury by regulating cell death through the direct repression of pro-inflammatory P2X7 in cardiomyocytes [115].

Therefore, purinergic signaling may be a potential mechanism of some pharmacological interventions. Metformin, a beneficial medicine for diabetes, can preserve myocardial function after ischemia and reduce infarct size. However, this effect could be completely abolished by a P1 receptor antagonist, which verifies the critical dependence of metformin on the stimulation of the P1 receptor [116]. Cilostazol, an anticoagulant drug, can reduce the myocardial infarct size by increasing ADO and NOx levels, attenuating superoxide production, and opening the mitochondrial K_{ATP} channels [117]. A clinically usable nucleoside transport inhibitor, dipyridamole, exerts a sustained cardioprotective effect via A1 receptor signaling during ischemia [118]. Moreover, opioid receptors interact closely with P1 receptors. For example, intrathecal morphine preconditioning can be used to reduce the infarct size in MIRI, but the cardioprotective effect can be reversed by the intravenous and intrathecal administration of a P1 receptor antagonist [119]. In induced postconditioning, an ultra-short-acting opioid receptor agonist, remifentanil has cross-talk with the P1 receptor [120]; both of these conditioning types depend on mitochondrial K_{ATP} and ROS in MIRI [121].

In light of these converging pathways between purinergic signaling and other pathways, the coadministration of multiple drugs will undoubtedly enhance the cardioprotective effect against MIRI. One study revealed that there is an additive effect on local myocardial adenosine levels in ischemia–reperfusion injury when ticagrelor and rosuvastatin are coadministered, which may be mediated by adenosine-induced effects, including the downregulation of pro-inflammatory mediators and upregulation of anti-inflammatory ones [122]. Another study reported that the caspase-1 inhibitor VX-765 combined with the P2Y12 receptor antagonist cangrelor, both administered at the reperfusion stage in MIRI, can preserve cardiac function and reduce infarct size after reperfusion [123]. The pre-ischemic coadministration of the sodium–hydrogen exchanger inhibitor cariporide and the adenosine agonist AMP579 can act additively to reduce the myocardial infarct size [124]. In addition, triple combining interventions by cangrelor, cariporide, and cooling can increase greatly myocardial salvage with an infarct size of only 3%, which is much better than the effect of two drugs used alone [125].

Other therapies

Beside the traditional ischemic conditioning and pharmacological intervention against MIRI, some novel therapies have been developed in recent years, which often exhibit significant cardioprotective effects; however, their underlying mechanisms have not been fully explored and explained. Fortunately, purinergic signaling may provide a novel reference for their interpretation. For instance, the mycelia of cultured *Cordyceps sinensis*, which is a Chinese herb frequently used, have a suppressive effect on ischemic contracture. Additionally, they provide cardioprotection through enhancing P1 receptor activation in MIRI [126]. Furthermore, resveratrol (a polyphenol produced in grapes and present in wine) can protect the heart from MIRI in the long term, by stimulating the production of ADO and activating A1 and A3 receptors [127].

It is worth noting that the cardioprotective effect of purinergic signaling also can be influenced by other active ingredients. One study showed that caffeinated coffee can abrogate the infarct size limiting effect of atorvastatin by blocking the P1 receptors and preventing the phosphorylation of Akt. However, caffeinated coffee does not affect the infarct size of rats not treated with atorvastatin [128]. A previous research suggests that alcohol consumption can mimic the cardioprotective effect of preconditioning by the

A1 receptor [129]; this effect warrants reconsideration and further research.

Purinergic signaling is also involved in other complementary therapies. As early as the 1990s, researchers found that ADO can affect coronary vasodilation during exercise [130]. Recent studies have shown that aerobic exercise can reverse cardiac remodeling by reducing inflammation, fibrosis, and apoptosis, thereby partly inhibiting P2X7 receptor expression in cardiomyocytes [131]. Acupuncture preconditioning has been verified as a potential therapy for MIRI, owing to its popularity in Asian countries [132, 133]. This potential mechanism of treatment requires further exploration. Purinergic signaling has been considered the initiation pathway in acupuncture therapy since 2009 [134–136]. Many researchers believe that purinergic signaling may be the regulatory target of acupuncture preconditioning for MIRI [137, 138], and electro-acupuncture may achieve a cardioprotective effect by modulating the expression of A2A and A2B receptors in myocardial tissue [139].

Reflection and prospect of purinergic signaling against MIRI

Based on this review, it can be suggested that purinergic signaling plays various roles in the pathophysiology of MIRI. ATP is released from ischemic cardiomyocytes in the form of autocrine or paracrine messengers, then activates P1 and P2 receptors, and mediates a series of pathological reactions. By the mutual promotion and inhibition in the corresponding relationships in different stages, these reactions are not isolated. They promote and inhibit each other and then play a corresponding role in different stages. During the ischemic phase, continuous local ischemia and hypoxia weaken the level of cellular oxidative phosphorylation and lead to energy exhaustion, due to which cellular energy demands remain unmet. At the same time, intracellular anaerobic glycolysis increases significantly to maintain ATP levels, thereby resulting in lactic acid accumulation and cell solute acidification. The activity of sodium-hydrogen exchange, sodium-calcium exchange, and calcium channels in the sarcoplasmic reticulum decreases, which leads to intracellular calcium overload. Subsequently, the cardiac cytoskeleton is depolymerized, and apoptosis and necrosis pathways are activated. All these activities result in metabolic collapse and myocardial cell death. Although the supply of oxygen and nutrients is restored during the reperfusion stage, a second wave of damage is induced. On the one hand, large numbers of peroxides are produced to damage the DNA and membrane structure through lipid peroxidation. They also initiate a variety of intracellular signal transduction pathways and induce the release of pro-inflammatory factors. On the other hand, persistent calcium overload activates the opening of the mPTP, again affecting energy production. This results in either apoptotic or necrotic cell death being induced. After 4 days of reperfusion, the damaged vascular endothelial cells release multiple chemokines, which cooperate with inflammatory factors and immune cells. These substances act on fibroblasts to initiate tissue remodeling and promote cardiac function recovery. During this complicated process, scientists first concerned the function of P1 receptors, which may be due to the modulative effect of ADO has been observed as early as the 1920s. Compared to ATP and ADP, the molecular structure of ADO is more stable. The mechanism of the A1 subtype is clearly demonstrated, which reveals that it is involved in many critical pathological links in MIRI, especially calcium overload, oxidative stress injury, and the opening of mPTP. Intracellular signaling pathways include PKC, PI3 kinase, and MAPKs. However, other subtypes of P1 receptors are involved in the inflammatory and immune pathways in MIRI. In particular, the A_{2b} receptor, which can only be activated under hypoxic conditions, shows a strong cardioprotective effect in MIRI. P2 receptors, such as P2X4, P2X7, P2Y2, P2Y11, and P2Y12 also play important roles in MIRI. They express in different cells and affect almost all the pathological links in MIRI. To some extent, regulating the activity of these P2 receptors to some extent can have a beneficial effect on ischemic cardiomyocytes. These compounds seem to constitute a class of promising therapeutic targets for MIRI. For example, targeting the P2Y12 receptor with clopidogrel, prasugrel, or ticagrelor is the most successful strategy to date.

Nevertheless, many aspects of purinergic signaling in regulating MIRI are still not fully understood due to a number of discrepant observations, which are as follows: (1) The essential function of purinergic signaling requires further accurate verification, in terms of the pathological link it acts on, the signaling pathway it is involved in, the species it works on, etc. These aspects should be conducted inspections in the future. (2) The MIRI is a complex process that lasts for a long time, including aggravating injury, self-healing, and recovery period, respectively. Thus, one receptor may play different roles at different stages in MIRI. Temporal changes of purinergic signaling require additional attention. (3) Purinergic signaling cross-talks with other signaling pathways. For example, several studies have reported the cardioprotective properties of P2Y12 receptor inhibitors, irrespective of their antithrombotic activity. The interaction effect among signaling pathways is also very important and can help predict the therapeutic potential and possible side effects. (4) Some non-drug interventions, such as ischemic conditioning, exercise, and acupuncture, are with powerful cardioprotective effects mediated by purinergic signaling. This

may depend on the integrative effect of multiple receptors expressed both in the cardiovascular and nervous systems; this needs to be researched further and verified clinically.

Author contribution Yi Zhuang, Mei-ling Yu, and Sheng-feng Lu discussed the concepts, contributed to literature and analysis, and wrote the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No. 81774210), "Six Major Talent Summit" of Jiangsu Province (YY-033), "Qing Lan Project" of Jiangsu Province (2020), and Acupuncture & Chronobiology Key Laboratory of Sichuan Province (No. 2021005).

Data availability Not applicable.

Declarations

Ethical approval Not applicable.

Informed consent Not applicable.

Conflict of interest The authors declare no competing interests.

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